Advances in Pemphigus and Pemphigoid

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Autoimmune blistering diseases: clinical advances from basic research

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The initial discovery, by immunofluorescence, of autoantibodies in pemphigus and pemphigoid was critical in allowing us to dissect the pathophysiology of these diseases. The understanding that these autoantibodies are pathogenic, either directly or indirectly, then led to advanced techniques for diagnosis, prognosis, and therapy. In pemphigus, patients' antibodies were used to clone the antigens, desmoglein (Dsg) 3 and desmoglein 1. Once cloned, these molecules were used to develop an ELISA test that has shown to be valuable in diagnosis and prognosis. Subsequently, a mouse with a genetic deletion of Dsg 3 was engineered and has been used to develop an active mouse model of pemphigus, which has in turn been used to further dissect the pathophysiology of disease and test innovative therapies. Furthermore, the cloned antigens have been used to study the T cell involvement in disease, which may lead to T cell therapy. The antigens have also been used to clone human monoclonal antibodies from patients that have the potential to be useful for targeted therapy. Additional studies of signal transduction in disease have suggested such pathways for another type of targeted therapy. Similarly, the cloning of pemphigoid antigen and the antigens of epidermoysis bullosa acquisita and cicatricial pemphigoid have given us reagents to develop new diagnostic and therapeutic approaches. These observations point out the very long lag time between discovery (immunofluorescence in 1964) and clinical advances (still continuing in 2006) from that discovery.

Pemphigus

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Pemphigus vulgaris (PV) is an autoimmune bullous disease caused by IgG autoantibodies against desmoglein 3 (Dsg3). Previously we have generated an active disease model for PV by a unique approach by adoptive transfer of Dsg3-/- lymphocytes to mice expressing Dsg3. To explore the pathophysiological mechanism of autoantibody production in pemphigus, we are investigating B cells as well as T cells specific for Dsg3 in mice. For B cell approach, we have generated Dsg3-specific AK7 B cell transgenic mice and found that Dsg3-specific AK7 B cells were detected in peripheral lymphoid organs without elimination or inactivation. However, when AK23 mAb that is pathogenic and able to induce blisters was injected into AK7-Tr mice, AK7 B cells disappeared from the peripheral lymphoid organs within a week following development of PV phenotype. In contrast, when non-pathogenic AK7 or AK9 mAb was injected, there was no disappearance of AK7 B cells. This finding suggests a novel tolerance mechanism of eliminating self-reactive B cells induced by danger signals from the skin. For T cell approach, we have isolated and characterized Dsg3-reactive CD4+ T cell clones. In autoantibody-mediated autoimmune diseases, T cells were characterized only by reactivity to autoantigens. In our passive transfer PV model, we are able to determine whether isolated T cells clones are directly involved in the production of pathogenic anti-Dsg3 IgG. The individual T-cell clones together with Dsg3-/- splenic B cells were transferred into Rag2-/- mice. Some T cell clones were able to induce the PV phenotype, while the others fail to do so. Further characterization of pathogenic and non-pathogenic Dsg3-specific T cells will clarify uncovered mechanisms involving T cells in autoantibody production in pemphigus.

Bullous pemphigoid

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Bullous pemphigoid (BP) is an autoimmune subepidermal blistering disease characterized by an inflammatory infiltrate and autoantibodies against the hemidesmosomal components BP230 (BPAG1) and BP180 (BPAG2 or type XVII collagen). In vitro studies show that total BP autoantibodies and affinity-purified BP180-specific autoantibodies induce dermal-epidermal separation in the presence of complement and neutrophils. In the rabbit anti-murine BP180 (mBP180) IgG passive transfer model of BP, subepidermal blistering is triggered by anti-mBP180 IgG and is dependent on the classical pathway of complement system. The classical pathway activation leads to mast cell degranulation and subsequent neutrophil infiltration. Neutrophil elastase, MMP-9 and plasmin released by neutrophils and other local cells damage BP180 and other extracellular matrix components, resulting in BP blisters. To directly test the pathogenicity of anti-BP180 autoantibodies, we generated a mouse strain in which the mouse BP180NC14A is replaced with the human BP180NC16A, a domain harboring BP dominant epitopes. The humanized BP180NC16A mice injected with BP180NC16A-specific BP autoantibodies developed skin lesions that mimics human BP and the rabbit anti-mBP180-induced BP clinically and immunohistologically. These animal models help us dissect disease immunopathology and develop new therapeutic strategies for BP.

Human Bullous Pemphigoid Antigen 2 Transgenic Skin Elicits Specific IgG in Wild Type Mice

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Bullous pemphigoid antigen 2 (BPAG2) is targeted by autoantibodies in patients with bullous pemphigoid (BP) and absent in patients with one type of epidermolysis bullosa. A keratin 14 promoter construct was used to produce transgenic (Tg) mice appropriately expressing human BPAG2 (hBPAG2) in murine epidermal basement membrane (BM). Grafts of Tg skin placed on gender-matched, syngeneic wild type (Wt) or MHC I −/− mice elicited IgG that bound human epidermal BM and BPAG2. Production of such IgG in grafted mice was prompt (detectable within 16+2 days), robust (titer>1280), durable (present >380 days), and correlated with the involution and loss of Tg skin grafts. MHC II −/− mice grafted with Tg skin did not develop anti-hBPAG2 IgG or graft loss indicating that MHC II:CD4+ T cell interactions were crucial for these responses. Tg skin grafts on Wt mice developed granulocyte-rich infiltrates, dermal edema, subepidermal blisters, and deposits of immunoreactants in epidermal BM. This model shows fidelity to alterations seen in patients with BP, has relevance to immune responses that may arise in patients with epidermolysis bullosa following BPAG2 gene replacement, and can be used to identify interventions that may block production of IgG against proteins in epidermal BM.

T cell control in pemphigus and pemphigoid

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Current concepts support the idea that autoaggressive T helper cells are critical players in the immune pathogenesis of pemphigus vulgaris (PV) and bullous pemphigoid (BP) by fostering auto-ab production by auto-aggressive B cells. Activation of autoreactive T cells in PV and BP is restricted by distinct HLA class II alleles that are prevalent in individuals with these disorders. Autoreactive T cells are not only present in patients but can be also detected in healthy individuals that carry the disease-associated HLA class II alleles. Recently, a subset of autoreactive T cells with remarkable regulatory function was identified in healthy individuals and to a much lesser extent in patients with PV suggesting that the occurrence of autoimmune bullous disorders may be linked to a dysfunction of regulatory T cells. These findings suggest that PV is presumably the consequence of a loss of tolerance against desmogleins on the B cell rather than the T cell level. In PV and BP, autoreactive T cells recognize restricted epitopes of the desmogleins and of BP180/BP230, respectively, that are also targeted by autoreactive B cells. Intimate T/B cell interaction is required for autoantibody production because depletion of B cells by the anti-CD20 monoclonal antibody, rituximab, also modulates the activation of autoreactive Th1 and Th2 cells in PV. The prompt clinical response of PV patients on rituximab treatment which is often seens prior to a decrease of serum autoantibodies may thus be related to an inhibitory effect on autoreactive T cells. There seems to be an equilibrium of autoaggressive Th2 and regulatory T cells because antisense-induced inhibition of the regulatory gene, Foxp3, leads to a phenotype typical for Th2 cells. The availability T cell-specific markers, such as HLA-DRß*0402-Dsg-tetramers, will hopefully facilitate to monitor autoreactive T cells and may thus serve as a sensitive marker for autoantigen-specific immune interventions.

Apoptosis in Pemphigus

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Apoptotic keratinocytes are present in perilesional, yet undetached, pemphigus skin. We have also shown that pemphigus sera from untreated, but not from steroid treated patients induce apoptosis in cultured keratinocyte. FasL levels are strikingly increased in sera from untreated pemphigus patients, as compared to either treated patients or controls. Pemphigus sera-induced keratinocyte apoptosis is partially prevented by pretreatment with either caspase-8 inhibitor or anti-FasL neutralizing antibody. Moreover, caspase-8 cleavage induced by untreated pemphigus sera is partially inhibited by anti-FasL antibody. Finally, untreated pemphigus sera or rFasL induce the cleavage of desmoglein 3 (dsg 3). Taken together these results suggest that, in pemphigus, keratinocytes undergo apoptosis before detachment, and that increased levels of FasL in pemphigus sera stimulate the activation of the caspase-8 extrinsic apoptotic pathway and the cleavage of dsg 3. Immunoglobulin Therapy (IVIg) down-regulate apoptotic genes and prevent acantholysis both in vitro and in vivo, thereby ameliorating pemphigus.

Autoantibody profile and epitope spreading in bullous pemphigoid

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Bullous pemphigoid (BP) is an autoimmune subepidermal bullous disease associated with circulating and tissue-bound autoantibodies recognizing an hemidesmosomal component, BP180 antigen. BP patients' sera contain IgG autoantibodies mainly directed to an extracellular immunodominant region, the NC16A domain, but also to additional antigenic sites located both in the intracellular and extracellular domains of BP180. Using a random epitope library displayed on λphage, we have selected several BP180 epitopes that are significantly recognized by BP sera. In addition, specific autoantibody reactivity has been associated with different clinical phenotypes and disease severity. To investigate the dynamics of the humoral immune response against BP180, we have then employed an experimental mouse model in which the skin of transgenic mice expressing the human BP180 molecule in the epidermal basement membrane is grafted onto syngeneic wild type animals, generating a specific anti-BP180 immune response. Evaluation of the reactivity of grafted mice sera against several BP180 epitopes at different time points after grafting showed the frequent development of an intramolecular epitope spreading phenomenon against human BP180, with recognition of extracellular domain epitopes preceding that of intracellular ones. In parallel, analysis of data from a prospective multicenter study of BP autoantibody profile in disease course indicated that reactivity against multiple epitopes, including intracellular ones, is already present at diagnosis in the majority of BP patients and that an ''epitope spreading phenomenon'' occurs in some patients during disease course. Altogether these findings support the current view that the humoral immune response against BP180 in BP at first targets extracellular epitopes which appear crucial to disease development, and suggest that ''epitope spreading'' is an early phenomenon which can occur at disease onset or even in the prodromal disease phase. Further studies are needed to assess the possible role of these additional antigenic sites in disease pathogenesis.

The ''Basal Cell Shrinkage'' Hypothesis - A New Explanation For Acantholysis In Pemphigus Vulgaris

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We propose a new hypothesis to explain acantholysis in pemphigus vulgaris (PV) and its restriction to the basal cell layer. The current explanation for acantholysis, that it results from anti-desmoglein antibodies interfering with the adhesive properties of desmosomes, is not fully satisfactory. If correct, keratinocytes should separate first at the desmosomes where desmoglein 1 and 3 are located. The reverse actually occurs. By electron microscopy cells separate first in interdesmosomal areas, where there are no desmosomes. Even in the final stage of acantholysis when keratinocytes are fully separated, desmosomes can still be attached to each other at the end of stretched out portions of the cell membrane. In addition, the earliest morphological event in acantholysis is the separation and retraction of tonofilaments from desmosomes. Based on these observations, we propose that acantholysis results from the collapse of the cytoskeletal structure of basal keratinocytes. As a result, basal cells shrink and pull away from each other more strongly than desmosomes can hold them together.

We further propose that acantholysis is limited to basal cells because these cells shrink more than suprabasal keratinocytes. This could occur either because basal cells are less rigid and shrink more readily than suprabasal keratinocytes when their cytoskeleton is altered, because their cytoskeletal structure is altered to a greater extent by signaling events, or because different signaling events are triggered in basal cells when they interact with pemphigus antibodies.

We hope that by challenging current dogma this hypothesis will stimulate novel approaches to study the causes of pemphigus and open new avenues to treat the disease.

Genetic polymorphisms in pemphigus

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In most autoimmune diseases, environmental and genetic factors contribute to their susceptibility. Clues to the underlying genetic susceptibility should be provided by epidemiological studies, including differences in the prevalence in different populations and familiar aggregation. In pemphigus, a large body of data has accumulated which supports genetic predisposition, in particular concerning case-control studies which allow to test an association between a given risk factor and a disease. This approach consistently demonstrated that the MHC locus is associated with both pemphigus vulgaris and pemphigus foliaceus. PV was found to be associated with DR4 and DR14 and, more precisely, with DRB1*0402 and DRB1*1401 subtypes. Susceptibility to PF was correlated with the presence of DR4, DR14 and DR1 alleles but in contrast to PV no single allele was shown to be associated with the disease. Four informative microsatellite markers were also detected, mapping into an HLA-G gene. Among genes coding for molecule thought to play a role in the autoimmune process, the gene encoding the putative autoantigen could be polymorphic and then, involved in the disease susceptibility. A single silent T to C transition at position 809 of the coding sequence of *DSG1* was shown to be significantly more frequent in both French and Tunisian patients than in controls and, interestingly, a combination of HLA DR4 and C/C (809) genotype conferred a stronger risk of PF development than either alone. A similar association of 2 haplotypes of the *DSG3* gene was observed in PV in British and Indian populations. Other candidate genes, as *IGH* and *IGL* or cytokine genes were also demonstrated to be associated with pemphigus. In conclusion, pemphigus, like other autoimmune diseases are complex and polygenic disorders in which many genes, with various penetrance operate and interact to control the disease process.

Characterization of Novel Signaling Pathways Downstream of Non-desmoglein Targets of Pathogenic Autoantibodies In Pemphigus Vulgaris

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Although it is accepted that pemphigus antibody binding to keratinocytes (KC) evokes an array of intracellular biochemical events resulting in cell detachment and death, the triggering events remain obscure. It has been postulated that binding of pemphigus vulgaris IgG (PVIgG) to KC induces ''desmosomal'' signaling. Since in contrast to integrins and classical cadherins, desmogleins are not known to elicit intracellular signaling, and since PV patients also produce non-desmosomal autoantibodies, we investigated the roles of desmoglein (Dsg) 1 and 3 in PVIgG-induced signaling. The time-course biochemical and morphologic studies of KC treated with PVIgG demonstrated that the activity of src peaked at 30 min, EGFR at 60 min and p38 at 240 min. The src inhibitor PP2 decreased EGFR and p38 activities by ~50% and ~30%, respectively, indicating that in addition to src, binding of PVIgG to KC engages other signaling mechanisms. The shrinkage of KC (cell volume reduction) became significant at 120 min, keratin aggregation at 240 min, and an increase of TUNEL + KC at 360 min. Pretreatment of KC with PP2 blocked PVIgG-dependent cell shrinkage by ~30%, keratin aggregation by ~45% and TUNEL positivity by ~45%, whereas the p38 inhibitor PD169316 inhibited these effects by ~10%, ~20% and 70%, respectively. Transfection of KC with small interfering RNAs that inhibited expression of Dsg1 or Dsg3 proteins by >80%, in both cases blocked ~50% of p38 activity but did not significantly alter PVIgG-dependent raise in src and EGFR activities. These results indicate that activation of p38 is a late signaling step associated with collapse of the cytoskeleton and dissassembly of desmosomes caused by upstream events involving src and EGFR. Therefore, the early events appear to be triggered by non-Dsg antibodies.

Sustained expression of the proto-oncogene c-Myc in Pemphigus vulgaris: pathomechanism and diagnostic tool

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We recently reported that PV autoantibody binding to desmoglein (Dsg) 3 of keratinocytes triggers pathogenic nuclear c-Myc accumulation and hyperproliferation in skin and mucous membranes of pemphigus vulgaris (PV) patients. The cascade leading to *c-Myc* transcription ranges from a transient, enhanced turn-over of cell surface exposed, non-keratin-anchored Dsg3 and associated plakoglobin (PG), through to depletion of nuclear PG, and as one of the consequences, abrogation of PG-mediated *c-Myc* suppression. In human and canine PV patients (10/10) this results in pathogenic c-Myc overexpression and hyperproliferation in all targeted tissues, including the stem cell compartment. This phenomenon is specific for PV as it is not observed in other autoimmune bullous diseases, skin disorders with known hyperproliferation, or toxic epidermal necrolysis (TEN), a clinically relevant differential diagnosis of PV. Moreover, disease progression in a patient with co-existing PV/pemphigus foliaceus (PF) correlated with nuclear c-Myc accumulation in keratinocytes that was detectable before the formation of typical acantholytic blisters, and significantly decreased upon successful treatment with systemic glucocorticosteroids. Together these data provide a novel insight into PV pathogenesis that combine the steric hindrance/cell signaling hypothesis mediated *via* soluble Dsg3/PG and further identify novel therapeutic targets and diagnostic tools.

New Diagnostic Tools in Pemphigus

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Pemphigus includes pemphigus foliaceus (PF) and mucosal dominant type and mucocutaneous type of pemphigus vulgaris (PV), as well as paraneoplastic pemphigus (PNP) and IgA pemphigus. By enzyme-linked immunosorbent assay (ELISA) using baculoproteins of human desmoglein 1 (Dsg1) and Dsg3, PF reacts with only Dsg1, mucosal dominant type of PV reacts with only Dsg3, and mucocutaneous type of PV reacts with both Dsg1 and Dsg3. Immunoprecipitation of Dsg3 swapped molecules using Dsg2 as a backbone has recently been developed. This study is useful for determining the epitopes for PV sera. PNP react strongly with both envoplakin and periplakin by Immunoblotting using epidermal extracts. By Immunoblotting using domain specific recombinant proteins of envoplakin and periplakin, PNP sera were shown to react with various domains of the two molecules. cDNA transfection test to COS-7 cells using cDNAs of human desmocollin 1 (Dsc1)-Dsc3 showed that subcorneal pustular dermatosis type of IgA pemphigus react with Dsc1. In addition, ELISA using baculoproteins of Dsc1-3 can be used to detect anti-Dsc autoantibodies in the sera of some atypical cases of pemphigus.

New diagnostic tools in bullous pemphigoid: practical use and limitations of BP180- and BP230-ELISA

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Enzyme-linked immunosorbent assays (ELISA) have recently been developed that allow the rapid and easy detection of circulating autoantibodies against BP180 or BP230 in bullous pemphigoid (BP). Since strong evidence exists indicating that anti-BP180 autoantibodies are pathogenic, the investigators' interest has focused on BP180. Specifically, the membrane-proximal NC16A domain on the ectodomain of BP180 has been recognized to contain the immunodominant antigenic sites. Therefore, most studies on the use of ELISA in BP have employed recombinant proteins consisting of the NC16A domain of BP180 with or without other portions of its ectodomain. Overall, the obtained data indicate that: (1) BP180-ELISA exhibit high sensitivity and specificity and are superior to conventional diagnostic tools (i.e., immunofluorescence and immunoblotting studies); (2) levels of anti-BP180 autoantibodies reflect disease severity and tend to parallel activity in the course of the disease; (3) the reactivity profile with distinct BP180 epitopes is associated with distinct clinical phenotype (e.g. mucosal involvement); (4) BP230-ELISA are less performant, but have confirmatory diagnostic value. Nevertheless, there are a number of key questions that remain unanswered concerning the practical usefulness of BP180-ELISA: (1) in differentiating BP from other pruritic eruptions frequently occurring in elderly; (2) in patients' management and guiding therapy when compared to obvious clinical symptoms (e.g. itch); and (3) in predicting relapse. It is hoped that the undergoing prospective studies in large cohorts of BP patients will provide better insights into the value of these tests.

Randomized controlled trial of adjuvant oral dexamethasone pulse therapy in pemphigus vulgaris (PEMPULS trial)

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Background: Evidence for the adjuvant effect of high-dose-corticosteroid pulse therapy in the treatment of pemphigus vulgaris is lacking by randomized controlled trial.
Objective: To determine the therapeutic effect of adjuvant dexamethasone pulse therapy when given in addition to conventional treatment.
Design: A randomized placebo-controlled trial.
Setting: International European multi-center outpatient and inpatient study.
Patients: Of the 20 enrolled patients, 11 were randomized to the dexamethasone pulse (DP) group and 9 to the placebo pulse (PP) group.
Interventions: Oral dexamethasone 300 mg pulses or placebo pulses 3 days per month. During the intervention, both DP and PP groups received conventional treatment with prednisolone 80 mg/day tapered over 19 weeks and azathioprine 3 mg/kg/day until end of study. Monthly pulses were continued until prednisolone was tapered to zero.
Main outcome measures: Number of patients in remission, the time to and duration of remission, cumulative prednisolone dose, and occurrence of adverse events during one year of follow up.
Results: Eight of 11 patients treated with DP and all nine with PP reached remission. Mean time to remission was 173 days with DP and 176 days with PP. The mean duration of remission within the first year was 151 days for DP and 141 days for PP. Mean cumulative prednisolone dose was 5300 mg in DP and 4882 mg in PP. Weight gain (>5% of baseline) occurred in 8 patients treated with DP, versus one patient on PP ($P<0.01$). No statistical significant difference ($P>0.05$) of an adjuvant effect of DP on remission of pemphigus vulgaris was found.
Conclusion: In new pemphigus vulgaris patients, there was no benefit of adjuvant oral dexamethasone pulse therapy given in addition to conventional treatment.

Rituximab in Pemphigus – German experience

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The treatment of severe, potentially life-threatening autoimmune blistering disorders such as pemphigus is still challenging. In the pathogenesis of autoantibody mediated diseases B cells are thought to play a decisive role. Thus, eradication of auto-reactive B cell clones, which we could recently demonstrate in the peripheral circulation for the major pemphigoid antigen Nc16a, might be an attractive therapeutic option. To deplete disease causing B cells that are involved in autoantibody synthesis, we have treated pemphigus patients with the monoclonal antibody rituximab directed against the B-lymphocyte surface antigen CD20. The significant clinical improvement in all patients after rituximab was accompanied by a marked reduction of the immunosuppressive co-medication. Rituximab treatment was well tolerated, adverse effects such as nausea, vomiting, facial edema, chills or cough occurred mostly during the first intravenous administration. Depletion of CD20 lymphocytes occurred rapidly after the infusion of rituximab and was long-lasting. However, the antibody titre to desmogleins correlated only in some patients with clinical improvement. This points to additional effects of B-cell directed therapy on the autoimmune process observed also in other autoimmune diseases, which to date are only poorly understood. In conclusion, clinical data reported by several groups indicate that B-cell directed therapy may represent a major step forward in the treatment of pemphigus.

Immunoadsorption in Pemphigus

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Pemphigus represents a group of potentially life-threatening, chronic skin diseases characterized by autoantibodies directed against desmoglein 1 and 3, transmembranous components of the desmosomes. There is profound clinical and experimental evidence for the pathogenicity of desmoglein-reactive IgG autoantibodies. Despite the use of high-dose glycocorticoids combined with immunosuppressive adjuvants, the treatment of pemphigus remains a challenging problem. The therapeutic removal of serum IgG by immunoadsorption has been proven to be effective in the treatment of severe pemphigus. In a recent study we could show that immunoadsorption using the synthetic ligand PGAM 146 (Globaffin®) with a high affinity for the Fc-portion of human IgG is capable of reducing the level of desmoglein-specific serum IgG by 70–80% in one treatment cycle consisting of four immunoadsorptions on consecutive days. Immunoadsorption has been applied in an adjuvant treatment regiment combined with high-dose glycocorticoids (1–2 mg/kg/d) and immunosuppressive adjuvants mostly mycophenolate mofetile or azathioprine. Compared to the conventional immunosuppressive treatment, the dose of systemic glycocorticoids can be tapered significantly faster after immunoadsorption. Especially patients with high autoantibody titres who are resistant to conventional treatment show good clinical responses to immunoadsorption. Recently the monoclonal anti-CD20 antibody rituximab demonstrated excellent clinical results in treating patients with recalcitrant pemphigus. Thus current investigations evaluate the combination of rapid removal of autoantibodies by immunoadsorption followed by B cell depletion using the anti-CD20 antibody to obtain long term control of the disease. In conclusion, immunoadsorption has proven to be a safe and well tolerated therapeutic option in the treatment of severe pemphigus.

ABSTRACTS

Intravenous Immunoglobulin (IVIg) Therapy in autoimmune mucocutaneous blistering diseases (AMBDs): Is there evidence-based efficacy?

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The purpose of this study is to determine if the current information on the use of IVIg in AMBDs demonstrates that it is evidence based effective therapy. This was accomplished by defining evidence based medicine. Then a sequential analysis was performed. The first step required formulating a question. The question for this evidence based examination of data on IVIg was: Is there evidence that IVIg is efficient in treating patients with AMBDs? Only those patients were included, in whom the diagnosis was based on histology and supportive immunopathological studies and in whom adequate follow-up was present. Then the evidence was researched. Thereafter the evidence was appraised for its validity. Several series of patients published in peer reviewed journals, on patients with pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, cicatricial pemphigoid and epidermolysis bullosa aquisita, were evaluated for the purpose of this study. A total of 175 patients were identified. Comparisons were made pre and psot IVIg therapy. These included: clinical response, recurrence rates, side effects from conventional immunosuppressive therapy (CIST), hospitalization, duration and frequency of remission and quality of life. Statistical analysis of these objective parameters indicated that IVIg was effective and superior to CIST. Further validation of the efficacy comes from those patients that discontinued IVIg therapy, and had recurrence of disease. In those who received IVIg again, recovery occurred. In those in whom it was not resumed, the disease progressed further. Recently pharmacoeconomic analysis has indicated that in the same patients, IVIg was cost-effective compared to CIST. Response to IVIg is not uniform. Based on clinical response, induction and maintenance of sustained remission, patients' maybe responders, partial responders or non-responders. In conclusion, the efficacy of IVIg for treating AMBDs is evidence based.

Defining clinical disease markers in pemphigus

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Pemphigus vulgaris (PV) is a rare, chronic, potentially life-threatening, acquired autoimmune vesiculobullous disorder. Although our scientific knowledge of PV is quickly advancing and our armamentarium of therapies is rapidly growing, there is still a pronounced lack of well-designed studies and evidence-based practice guidelines. This dearth is not surprising given the rarity of the disease, as well as the absence of common terms, endpoints, and measurements to assess disease extent, activity, severity, and therapeutic response. The recognized need for common definitions and measurements for PV was addressed during a workshop organized by Dr. Lowell Goldsmith and held at the international NIH Pemphigus meeting in June 2005. Subsequently, a PV Definitions Committee was organized and convened during the American Academy of Dermatology meeting in San Francisco held in March 2006. The committee was comprised of dermatologists with expertise and special interests in pemphigus. During the course of two days, there was (1) a systematic review of the terms and measurements used in the pemphigus literature and in ongoing PV studies, (2) an agreement regarding the definitions of endpoints, complete and partial remission, relapse/flare, and failure, and (3) an active discussion and proposals for common measurements of the extent of disease, disease activity, and the intensity of therapy. Those unable to attend the meeting were contacted by email. A consensus statement with the agreed upon definitions for PV is being developed. A subsequent meeting in May 2006 evolved options for disease activity and severity outcome measures. The formation of the PV Definitions Committee, a consensus statement with agreed upon common definitions, and the ongoing discussion and refinement of proposed common measurements for PV are the initial and necessary steps towards progress in the clinical evaluation and therapy of PV. Further progress and advancement will require a continued collaborative effort.